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ELECTRICAL STIMULATION FOR PHYSIOLOGIC MEASUREMENT OF NEUROMUSCULAR FUNCTION AND RESPIRATORY SUPPORT DURING ANTICHOLINESTERASE POISONING

ANNUAL REPORT

Edmund H. Yodlowski, Ph.D.

October 1, 1984

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ABSTRACT

Animal experiments have been conducted to implement and evaluate the transesophageal electrophrenic stimulation technique (TEST) for respiratory pacing. In these experiments, parameters for the TEST pacing method were evaluated to determine appropriate stimulation parameters to produce effective and efficient respirations. The effectiveness of TEST was determined by measuring diaphragm muscle contractile force, intrapleural pressures, inspiratory force, respiratory functions such as tidal volume and minute volume and blood gas partial pressures including pO_2, pCO_2, and pH.

FOREWARD

In conducting the research described in this report, the investigators have adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

STATEMENT OF THE PROBLEM

The purpose of this research is to develop the techniques necessary for providing short-term respiratory support for personnel poisoned by organophosphate agents. Following acute exposure to organophosphate compounds, respiration ceases before cardiovascular collapse occurs[1]. Consequently, military personnel exposed to these compounds in the field are most likely to die from asphyxiation.

The mechanism or mechanisms for respiratory arrest remain uncertain. By virtue of their ability to cross the blood-brain barrier[2] and inhibit cholinesterase activity[2,3], the organophosphates are capable of interrupting control of respiration either centrally (i.e. within the central nervous system) or peripherally by blocking neuromuscular transmission or contraction coupling at the peripheral muscles. Although organophosphates can block synaptic transmission at the neuromuscular junction, evidence[4,5] suggests that the peripheral neuromuscular junction may be more resistant to the effects of these organophosphate compounds than CNS synapses. It has been shown that efferent neural activity in the phrenic nerve is diminished following organophosphate poisoning[6] which supports the theory of a central nervous system cause for post organophosphate respiratory depression.

We hypothesize that it will be possible to overcome organophosphate induced respiratory arrest by providing artificial respiratory pacing. This research is aimed at producing a means of respiratory support via electronic stimulation of the phrenic nerve(s) that can be used when central respiratory drive has become blocked by organophosphate agents.

Cont'd

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METHODS

During the first contract year, the cat animal model to be used to test the hypothesis of electrophrenic stimulation during organophosphate poisoning was developed. In those studies, the normal values for tidal volume, respiratory rate, blood pressure, blood gases and pH were measured under the experimental conditions to be used to evaluate electrophrenic stimulation. Effectiveness of respiratory effort was measured in normal cats under the same conditions. Respiratory effort was assessed by measuring the maximum inspiratory pressure (MIP) and diaphragm muscle contractile force. During the second contract year, the subject of this report, additional studies establishing normal baseline values have been performed, and the stimulation technique to be used for respiratory pacing has been developed.

The method used for providing respiratory support utilizes electrical stimulation of the phrenic nerve. Rather than using electrical stimulation by means of an electrode placed directly on the phrenic nerve or other pacing methods such as intravenous electrodes, we have begun to evaluate transesophageal electrophrenic stimulation (TEST). In this method of phrenic nerve pacing, an electrode is passed into the esophagus and a second electrode is placed on the animal's chest wall. Because of the close proximity of the phrenic nerves to the esophagus, the current passing from the esophageal electrode to the external electrode will pass through the phrenic nerve, producing stimulation of the nerve.

The stimulus used for phrenic nerve pacing consists of regulated current pulses. The stimulators used in these experiments are capable of providing square regulated current outputs variable from 0 to 50 ma. Although the duration of the current stimulus pulse is variable from 0 to 200 msec, for these experiments the stimulus duration was maintained at a fixed value of 0.05msec. Stimulus amplitude and frequency were variable and their values adjusted either by control knobs on the front panel of the stimulator or through a digital/analog interface with a computer.

During this year our goal was to interface the programmable stimulator with the Apple computer used in the laboratory and through tests of various forms of stimulation patterns and electrode placement, to determine which conditions best simulate normal respiratory efforts and maximize ventilation.

A computer program written in Applesoft Basic, using a Mountain Hardware analog to digital (A/D) and digital to analog (D/A) converter board, was used to interface with the programmable stimulator. From the computer keyboard, stimulus amplitude, stimulation frequency and the frequency of the respiration can be rapidly changed. During normal respiration, the diaphragm muscle, the principal muscle of respiration, undergoes a gradual contraction followed by a period of relaxation. During inspiration, diaphragm contractions produced a negative intrapleural pressure causing an inward flow of air into the lungs. When the diaphragm relaxes, the elastic recoil of the chest and lungs allows the lungs to collapse; the air within the lungs is expired. If a tetanic electrical stimulus pulse train is applied to the phrenic nerves, a very rapid onset of diaphragm contraction results. The respiratory movements during such electrophrenic stimulation produce inspiration, but the respiratory

movements are much more like those of a hiccough. In order to simulate normal respiratory movements and smooth airflow, the onset of diaphragm contraction and diaphragm relaxation must be gradual.

In our experimental technique, a gradual increase in contractile response of the diaphragm muscle is produced by a gradual increase in stimulus amplitude. The stimulus amplitude is made to increase linearly over a variable interval of time. At the end of inspiration, diaphragm contraction is also decreased gradually by linearly decreasing the stimulus amplitude back to zero. An example of the envelope used for the stimulus amplitude is shown in Figure 1.

The "effectiveness" of respiration provided by TEST in our adult cat model was measured in several ways. We assessed how well the animal was being ventilated by measuring the minute and tidal volumes of air exchanged. Average respiratory minute volumes and tidal volumes were measured by collecting expired gas in a closed anesthesia bag over a period of 2 minutes. Minute and tidal volume measurements made before any experimental electrical stimulation of the phrenic nerve(s) served as baseline controls. Additional measurements were made just prior to and at least 5 minutes after changing phrenic nerve stimulation paradigms.

The strength of respiratory effort was determined by measuring the maximum inspiratory pressure (MIP) as well as the intrapleural pressure. The strength of the diaphragm contraction was determined by measuring the downward deflective force produced by the diaphragm muscle during stimulation. MIP was measured as the peak negative pressure generated in the trachea against an occluded airway. In those animals in which intrapleural pressure was recorded, the intrapleural pressure was measured by inserting a cannula into the intrapleural space. The cannula was a 20 gauge Intramedic Medicut cannula, which is a polyethylene tubing normally used for establishing intravenous or intrarterial lines. The cannula with its insertion needle was passed through the intercostal space between the seventh and eighth ribs at an angle of approximately 45 degrees relative to the chest wall. When the cannula was felt to pass through the chest wall, the needle was removed and the cannula connected to a pressure transduce (Gould #534464) and displayed on a Gould model 2400 strip chart recorder.

Seventeen adult cats of both sexes have been used in this study, to date. All animals were healthy and free from any obvious signs of neural, muscular or respiratory disease. Their weight ranged from 2.8 to 3.5 kg with an average of 3.0 Kg. The animals ere anesthetized by an intraperitoneal injection of sodium pentobarbital (40mg/Kg). An adequate level of anesthesia was determined by the absence of paw withdrawal reflex in response to pinching the paw. After an appropriate level of anesthesia was established, the animal was surgically prepared. An intravenous cannula was inserted into the femoral vein for administration of drugs. An arterial line for measuring blood pressure and sampling arterial blood (to measure pO_2, pCO_2 and pH) was inserted into the descending aorta through the femoral artery. A tracheostomy was performed and an endotracheal tube inserted into the trachea and tightly tied in place. Care was taken to ensure that there was no air leakage around the tubing in the trachea. In each animal being prepared

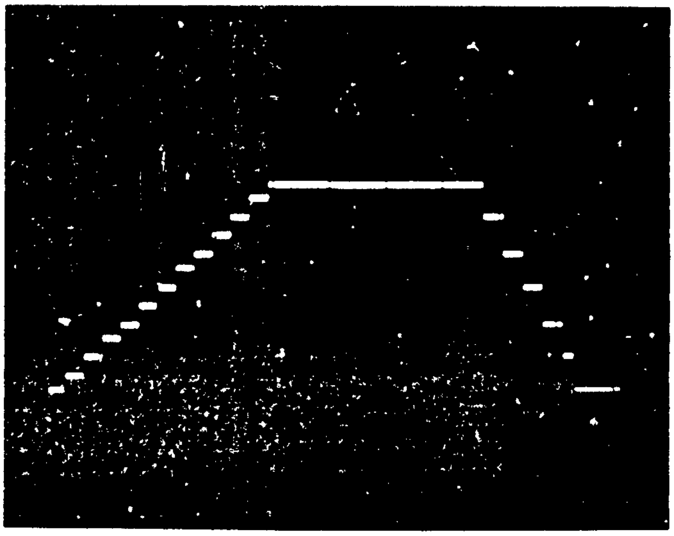

Figure 1

Photograph of an oscilloscope tracing showing the analog voltage delivered to the stimulator regulation stimulus output during TEST. Vertical deflection represents a voltage (0.5 v per chart division) proportional to the stimulus current amplitude and the time is displayed along the horizontal axis (0.2 msec/division).

The stimulus amplitude increases incrementally from zero to a predetermined peak value. In this example, the peak voltage (corresponding to the plateau) produced a 5 ma stimulus. The time for the rising phase (time to go from 0 to 5 ma) was set to 400 msec. The decreasing phase (time from peak to zero) was set to 200 msec. Total stimulation time was 1200 msec. Stimulation frequency was 30 Hz and respiratory rate was 20 breaths/min.

for direct stimulation of the phrenic nerves, each of the phrenic nerves was isolated bilaterally in the neck at a point just after the nerve exits from the thoracic cavity. The electrodes used for phrenic stimulation consisted of two wires wrapped around the phrenic nerve with a separation distance of at least 1.5mm. Dehydration of all exposed tissue was prevented by covering the tissue with saline soaked gauze pads.

The strength of a diaphragm contraction was measured by recording the downward deflective force produced during a diaphragmatic contraction. This force was measured using a cantilevered beam strain-gauge transducer. This method for measuring diaphragm force was described in detail in a previous report[7]. The abdominal side of the diaphragm was exposed by making a midline abdominal incision extending from the tip of the xyphoid to the umbilicus. The ligaments supporting the liver were severed, providing a clear exposure to the central tendon region of the diaphragm. One end of the force transducer was fixed to a rigid frame upon which the animal lay. A thin rod was connected to the other end. This assembly was positioned so that the free end of the rod pressed against the abdominal side of the diaphragm. The tip of the force transducer was placed against the diaphragm at the muscle-tendon interface (this portion of the diaphragm undergoes the greatest downward movement during diaphragm muscle contracture, and it provided us with the largest force values.) As the diaphragm contracted, it pressed against the rod, causing elastic deformation of the cantilever. Bending of the cantilever was measured by the strain gauges. This signal was amplified and displayed as a pen deflection on a strip chart recorder.

TEST was evaluated using the same parameters to assess the effectiveness of ventilation and diaphragm muscle contractions as were used for evaluating direct excitation of the phrenic nerves. TEST was evaluated after spontaneous respiration was obtained by an overdose of sodium pentobarbital. The sodium pentobarbital was administered intravenously until spontaneous respirations ceased. During TEST, minute and tidal volumes were measured, and periodic arterial blood samples were obtained for measurements of blood pH, pO_2, and pCO_2.

RESULTS

Direct stimulation of Phrenic Nerves

The purpose of the first series of animal experiments was to measure the diaphragm muscle force and inspiratory force that could be generated if one or both phrenic nerves were stimulated maximally. By stimulating the phrenic nerve directly, we were able to determine what the TEST technique should be able to produce under optimal conditions (i.e., stimulation of the whole nerve). Direct bilateral stimulation of the phrenic nerves produced a strong contracture of the diaphragm. The threshold for stimulation was typically 2 to 3 ma. When the stimulus amplitude was increased to more than 8 or 10 ma, collateral stimulation of brachial nerves often resulted. This collateral stimulation was probably due to "leakage" of electrical current around the electrodes. Maximal diaphragm force was typically produced with a stimulus amplitude of 5 to 7 ma.

The force we recorded and call the diaphragm force is not the true contractile tension developed by the diaphragm muscle but only the downward deflective component of that force. Nevertheless, we feel that it is a reasonable approximation of the true diaphragm contractile force and provides an accurate relative measure of that force. Furthermore, it is the downward deflection of the diaphragm which is largely responsible for the negative intrathoracic pressures that are developed during inspiration.

The diaphragm force generated during a spontaneous breath during quiet breathing is only a fraction of the total force that the diaphragm is capable of generating. In order to measure the maximum diaphragm contractile force, it was necessary to elicit a maximal breathing effort. A maximum effort was induced by first occluding the animal's airway. The peak downward deflective force of the diaphragm was measured during the first breath immediately following removal of the airway occlusion. The force was recorded after removal of the airway occlusion because when the airway is blocked, the negative intrathoracic pressure developed prevents the diaphragm from shortening and moving downward, thus the measured force is diminished, even though the true contractile force may be maximal.

Electrical stimulation of the phrenic nerve(s) produced a diaphragm contractile force greater than the animal's own maximal effort. Stimulation of the right phrenic nerve produced a stronger contraction of the diaphragm than did stimulation of the left phrenic nerve (using the same stimulation parameters). The force produced by unilateral stimulation of either phrenic nerve was less than that produced by bilateral stimulation. Furthermore, the response to bilateral stimulation was greater than (not merely equal to) the algebraic sum of the forces produced by the stimulation of each phrenic nerve individually. The data from these experiments are summarized in table 1. Figure 2 shows an example of the downward deflective force measured during spontaneous breathing and during unilateral and bilateral electrical stimulation of the phrenic nerve(s).

The maximum inspiratory pressure developed during bilateral electrical stimulation of the phrenic nerves was greater than that produced by spontaneous effort during quiet breathing but less than during a spontaneous maximal effort. The effects of phrenic nerve stimulation upon maximum inspiratory pressure are summarized in table 1. An example of a record of the inspiratory pressure measured during phrenic nerve stimulation and spontaneous efforts is shown in figure 3.

TRANSESOPHAGEAL ELECTROPHRENIC STIMULATION

The effectiveness of transesophageal electrophrenic stimulation (TEST) to provide respiratory pacing was evaluated in 7 cats. In all but two animals, TEST was able to maintain respiratory function and arterial blood gases within normal ranges. In one animal, the blood gas values continued to deteriorate, with marked hypercapnia and hypoxia. When the animal was placed on a positive-pressure ventilator, air could be heard escaping through a small pneumothorax which had been inadvertently created at the apex of the thoracic cavity where the left phrenic nerve passed from the thorax into the neck. In the other animal, adequate stimulation of the diaphragm could not be

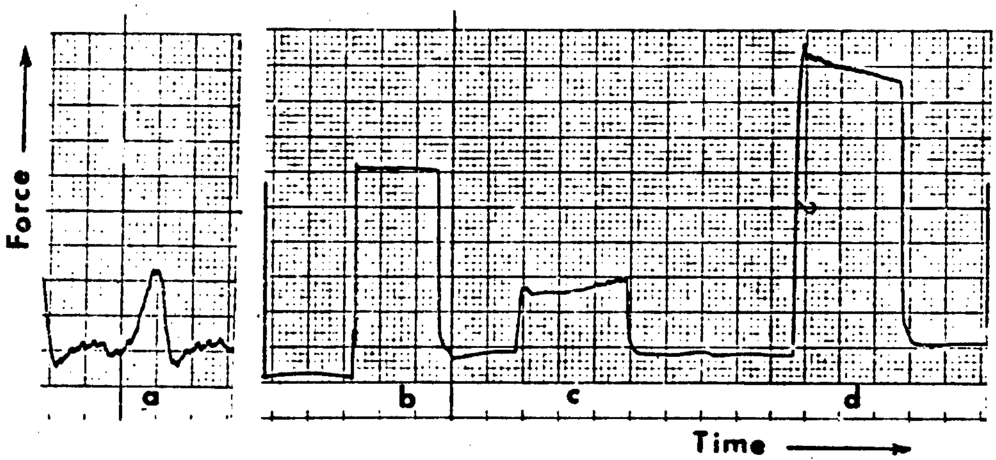

Figure 2

Tracing of the downward deflective force produced by contraction of the diaphragm in a cat. An upward pen deflection indicates a positive contractile force. The first peak (a) was recorded during a spontaneous breath; the second (b) was the response to electrical stimulation of the right phrenic nerve only; (c) was the response to stimulation of the left phrenic nerve only. Tracing (d) shows the response to bilateral phrenic stimulation. Th stimulus consisted of rectangular current pulses with a duration of 0.1 msec and an amplitude of 5 ma applied to the nerve for 5 seconds. Stimulation frequency = 30 Hz. Chart speed = 1 large division (5 mm)/sec.

	INSPIRATORY PRESSURE (cmH2O)	DIAPHRAGM FORCE g)
Spontaneous	-21.6	27.6
Left Phrenic Stimulation	- 7.8	24.0
Right Phrenic Stimulation	- 9.7	61.2
Bilateral Phrenic Stimulation	-23.3	102.0

Table 1

Comparison of the maximum inspiratory pressure (MIP) and diaphragm contractile force generated during an inspiratory effort. MIP was measured during airway occlusion. The MIP and diaphragm force produced during a spontaneous breath (i.e., a breath initiated by the central nervous system) are compared to the response elicited by direct electrical stimulation of the phrenic nerve(s).

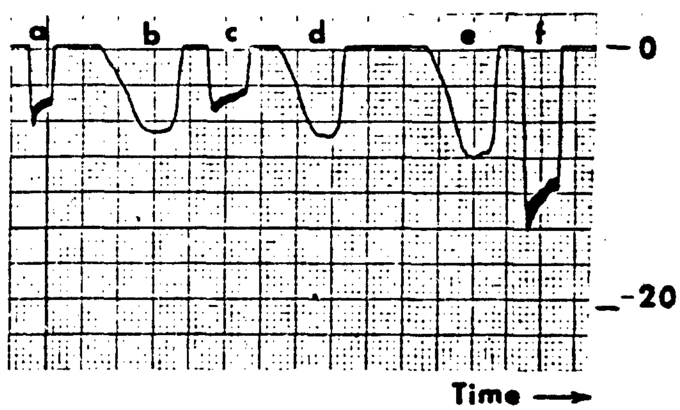

Figure 3

Tracing of maximum inspiratory force produced by spontaneous breathing effort and by direct electrical stimulation of the phrenic nerves. A downward pen deflection indicates increasing negative inspiratory pressure. Peaks b, d, and e were produced by a spontaneous effort by the cat. Peak a was produced by unilateral stimulation of the right phrenic nerve; peak c, by unilateral stimulation of the left phrenic nerve; and peak f, by bilateral phrenic stimulation. Stimulus amplitude = 5 ma; stimulation frequency = 30 Hz; chart speed = 1 large division (5 mm)/sec.

		BLOOD GASES & pH			TEST SETTINGS			
Time (min)	Tidal Vol. (ml)	pH	pCO_2 (mmHg)	pO_2 (mmHg)	TST (msec)	RAT (msec)	DAT (msec)	RR (breaths/min)
Control	44.3	7.377	26.8	90.1	----	----	----	28
+ 3	39.3	7.387	22.3	103.7	1500	500	200	28
+ 19	39.3	7.421	25.5	137.0	1500	200	200	28
+ 28	33.0	____	____	____	1500	200	200	28
+ 61	32.4	7.397	21.2	102.0	1500	200	200	25

Table 2

Data showing the changes in tidal volume and arterial blood gas partial pressures and pH measured in a cat in which respiration was paced using TEST. Central respiratory drive was blocked by a barbiturate overdose at time zero. Even though the tidal volume was less during TEST than it was during spontaneous breathing (control), the values for arterial blood gases were within normal limits. Respiratory rate (RR) was diminished after 30 minutes because of a developing alkalosis.

produced without stimulation of either the abdominal muscles or the muscles associated with the brachial plexus. Table 2 shows changes in tidal volume and arterial blood gas partial pressures and pH measured in a cat in which respiration was paced using TEST.

Figures 4 and 5 demonstrate the effects of increasing the frequency of stimulation during TEST upon diaphragm force and trachea airflow, respectively. Increasing stimulation frequency produced a successively stronger contractile response from the diaphragm, whereas the intrapleural pressure and airflow reached their maximum values at a frequency of 30 to 35 Hz and did not increase further as the stimulation rate increased. These results indicate that even though the diaphragm is "working harder" to produce stronger contractions, this respiratory effort is no more productive in ventilating the lungs than is that achieved at a stimulation rate of 30 to 35 Hz. Consequently, it is recommended that for all future studies using TEST, the stimulation frequency for excitation of the phrenic nerve not to exceed 30 to 35 Hz.

Experiments were conducted to determine the timing pattern for the phases of the TEST paradigm which would produce effective and efficient respiration.

The duration of diaphragm contracture during TEST is directly related to the duration of the electrical stimulation period TST. The duration of diaphragm contracture was determined to be also dependent upon the threshold level for electrical stimulation. Since the muscle contracts only when the stimulus is greater than threshold, the duration of the diaphragm contracture is indirectly related to the TEST parameters RAT, DAT and maximum stimulus amplitude because together they determine the proportion of the TST during which the stimulus amplitude exceeds the threshold level. Decreasing RAT or DAT increases the duration of contracture as does increasing the maximum stimulus amplitude level.

In the animals tested the stimulus amplitude of which the diaphragm began to contract ranged from 3.0 to 11.6 ma with a mean of 6.4 ma ± 3.2 ma (mean ± 15.0).

It was found that once excitation threshold was exceeded the force generated by the diaphragm rapidly rose toward its peak value. In some animals peak contractile force was reached before the stimulus had reached its maximum level. Unless RAT was longer than 450 msec the rate at which the diaphragm developed its peak contractile force was relatively insensitive to variations in RAT although as explained above these changes did affect the duration of the contracture.

Increasing the duration of TEST stimulation (TST) produces a longer diaphragm contraction but it does not necessarily improve ventilation. If the diaphragm contraction time exceeds the inspiration time the diaphragm continues to "work" without effectively moving air into the lungs. This results in a breathing pattern like that of a person who is holding their breath. An example of the change in tracheal airflow produced by changes in TST is shown in figure 6. Maximum inspiration (as indicated by a "no flow" condition in the trachea) is achieved much more quickly during TEST than

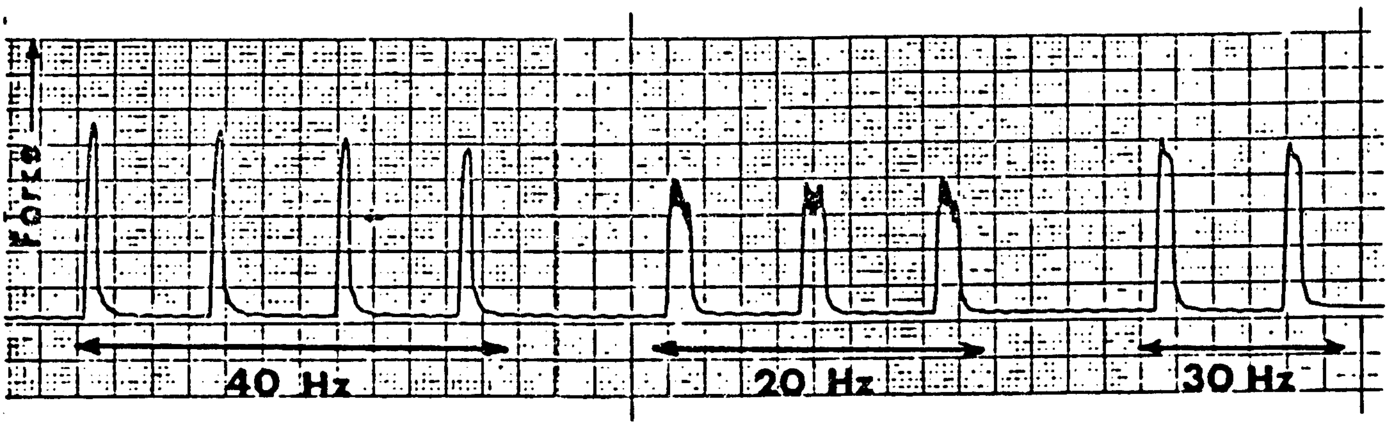

Figure 4

Tracings of the diaphragm force recorded from a cat during TEST under conditions of changing stimulation frequency. An upward deflection corresponds to a positive contractile force. The stimulus amplitude was 15 ma in all three tests. Total stimulation time (TST) = 1000 msec; rising amplitude time (RAT) = 500 msec; decreasing amplitude time, decreasing amplitude time (DAT) = 100 msec. Chart speed = 5 mm/sec (1 large division/sec); force calibrations: 1 large division (5 mm) = 7.5 g.

Note the stimulation at 20 Hz did not produce a fully fused contraction of the diaphragm. At 30 Hz the contraction was fused, but the peak force was not significantly greater than that at 20 Hz. Peak force was greater when the rate was increased to 40 Hz.

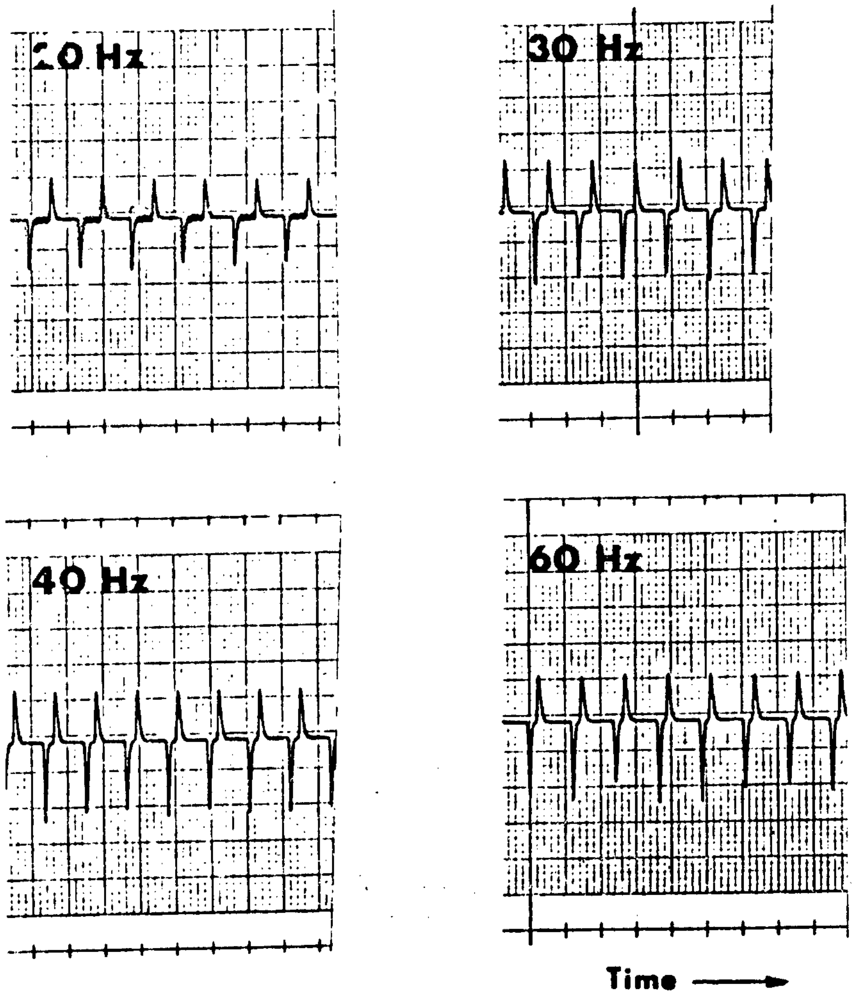

Figure 5

Tracings measured from a cat during TEST, showing the trachea pressures recorded when stimulation frequency was changed. A downward pen deflection indicates a negative airway pressure. Stimulus amplitude (15 ma) and stimulus pulse duration (0.1 msec) remained constant for all records. TEST variables (see Figure 4 legend): TST - 1000 msec; RAT = 400 msec; decreasing amplitude DAT = 200 msec. Chart speed = 2 mm/sec (2 large divisions/5 sec).

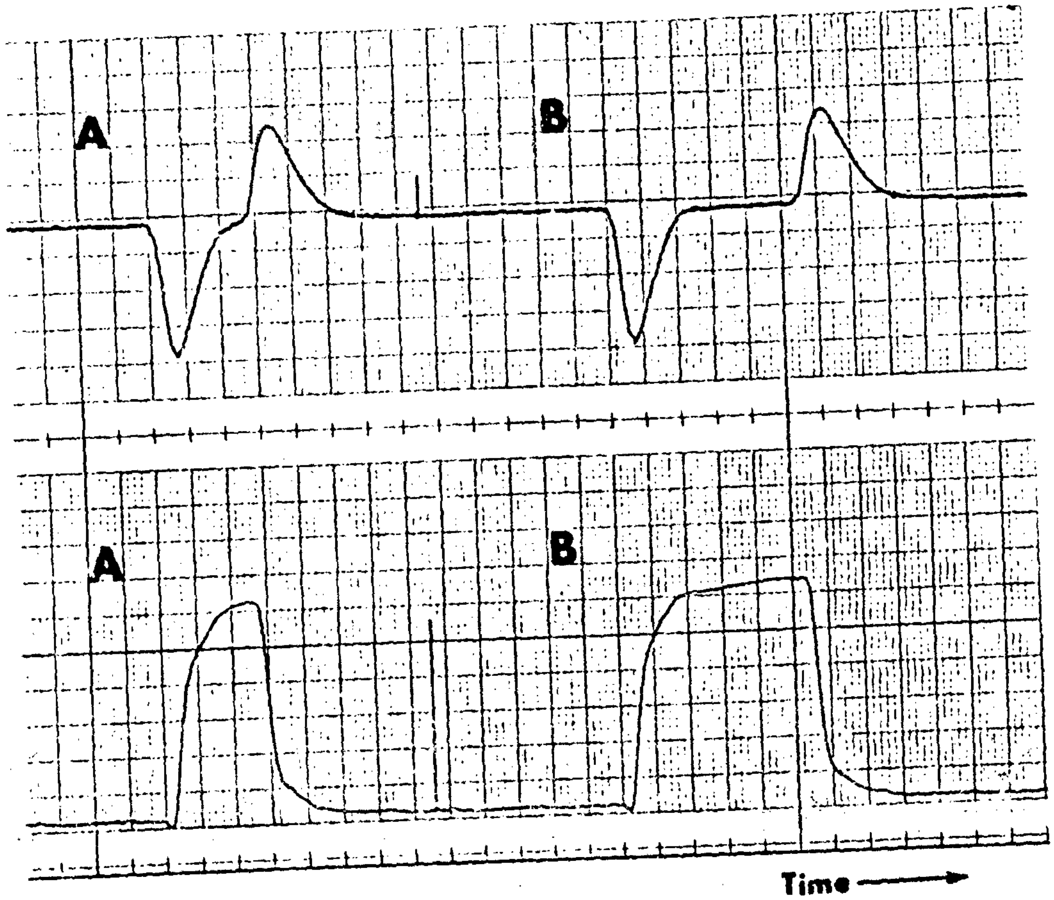

Figure 6

Recordings made during TEST, showing the effect of increasing the total stimulation time upon the diaphragm force (lower curve) and trachea airflow (upper curve). TST = 1000 msec (A), 1500 msec (B),; RAT = 450 msec (both); DAT = 200 msec (both). Peak stimulus amplitude = 15 ma. Stimulus frequency = 30 Hz. Chart speed = 25 mm/sec (5 large divisions/sec).

during spontaneous breathing (0.55±.15 sec vs 1.50±.37 sec respectively). The more rapid inspiration during TEST is attributable to the much more rapid diaphragm contraction once stimulation threshold has been reached.

In all animals TEST produced a more rapid diaphragm contracture than occurred during normal spontaneous breathing. During TEST the time required for the diaphragm to reach its peak force (i.e. the time to go from 0 to peak) was 0.23±.11 sec (mean ±1 SD). During spontaneous breathing, peak diaphragm force was reached after 1.14±.23 sec. Consequently TEST produced a much more rapid inspiration than occurs normally.

Contracture of the diaphragm induced by TEST produced corresponding changes in intrapleural pressure (IPP). IPP rapidly becomes negative as the diaphragm contracts and moves downward. Peak negative IPP was reached in 0.62±.52 sec during TEST. There was considerable variability between animals in records of the IPP. This variability was due in part to differences in chest wall rigidity, lung filling and catheter placement.

An example of the temporal relationship between the stimulus amplitude, IPP and diaphragm force is shown in figure 7. In this example, it can be seen that the stimulus amplitude increases briefly before there is a measurable contraction of the diaphragm or change in IPP. For this animal, when the stimulus amplitude reached 8.7 ma, the diaphragm force began to increase rapidly. At the same time, there was an increase in negative IPP. In figure 7 it can also be seen that IPP began to diminish even though the diaphragm remained contracted. Diaphragm force dropped rapidly when stimulus, which was probably due to filling of the lungs with air, amplitude had fallen to 8.7 ma as did the IPP.

CONCLUSIONS

The results of these experiments indicate that the force developed by the diaphragm during bilateral phrenic nerve stimulation, although not equal to that produced by spontaneous maximal respiratory effort, is capable of generating a diaphragm contracture adequate to provide a strong inspiratory effort. The force produced by phrenic stimulation is substantially greater than that normally generated during quiet, spontaneous breathing.

One of the important parameters for the implementation of TEST involves the relative times for the onset of a diaphragm contraction and relaxation. Contracture of the respiratory muscles causes the intrathoracic pressure to become less than atmospheric pressure, inducing air to fill the lungs. If the muscles remain contracted for only a short period of time, the lungs may not fill entirely. On the other hand, if the respiratory muscles (primarily the diaphragm) remain contracted even after the lungs have filled, no additional ventilation will occur. Transesophageal stimulation for a time period longer than necessary to fully inflate the lungs is nonproductive work. Prolonged stimulation is counterproductive to the extent that it produces a more rapid fatiguing of the muscle. Consequently, the ideal stimulus pattern will allow the diaphragm muscle to relax shortly after airflow into the lungs has ceased.

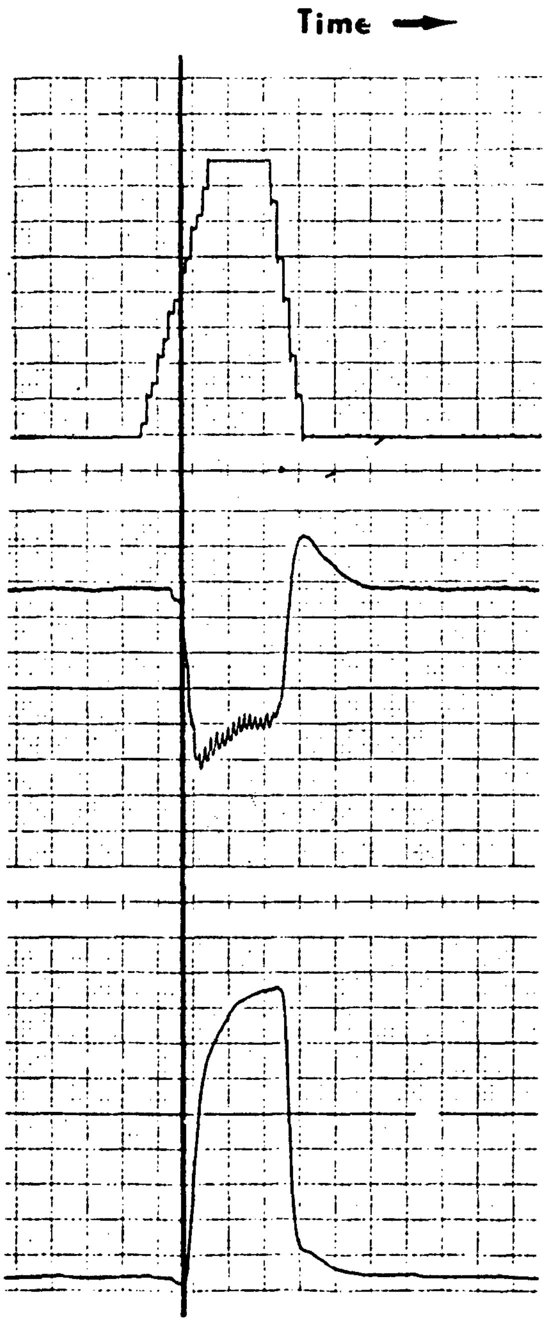

Figure 7

Tracings showing stimulus amplitude, intrapleural pressure (IPP) and diaphragm force recorded simultaneously during TEST. All three tracings were recorded simultaneously. The vertical line was drawn to show the point at which stimulation threshold was reached during TEST.

The upper tracing shows the changing stimulus amplitude during TEST. The maximal amplitude (during the plateau) is 15 ma.

The middle tracing shows the intrapleural pressure produced. A downward deflection indicates a pressure negative with respect to atmospheric pressure. The "jitter" shown in the IPP tracing is due to the heart beating. Pressure calibration: 1 large division (5mm) = 5 cmH_2O.

The bottom curve represents the diaphragm contractile force produced simultaneously with the intrapleural pressure above. Force calibrations: 1 large division (5 mm) = 7.5 g.

Chart speed = 25 mm/sec (5 large divisions/sec).

TST = 1000 msec
RAT = 450 msec
DAT = 200 msec.

In our studies, a stimulation interval of 1.2 seconds was normally sufficient for inhalation of a maximal tidal volume. Allowing a certain safety factor in order to overcome an increase in airway resistance, we found that the stimulation time should not exceed 1.4 to 1.5 seconds. Increasing stimulation time to more than 1.2 seconds did not increase the tidal volume or minute ventilation in normal unobstructed animals.

The data from these experiments have shown that TEST can be used to sustain homeostasis in an animal with central respiratory drive blocked by barbiturates. Normal tidal volumes and minute ventilation can be obtained by varying TEST stimulation parameters. In particular, if an obstruction of airflow is observed or anticipated (as would probably occur during organophosphate poisoning), increasing the duration of diaphragm stimulation will increase the inspiratory time, allowing more airflow. Using this technique, an adjustment of the maximal stimulus amplitude will produce a strong, near-maximal diaphragm contraction with each breath. Further increase in stimulus amplitude will not increase tidal volume but will probably produce unwanted excitation of other neighboring nerves, particularly those associated with the brachial plexus. Stimulus amplitude of less than 15 ma was sufficient to produce maximal diaphragm contractile force in the animals we studied.

Measurement of inspiratory force (MIF) during TEST has shown that the inspiratory force developed by transesophageal stimulation of the phrenic nerve is less than that which can be elicited by a maximal respiratory effort by the animal, but is comparable to that produced by direct stimulation of the phrenic nerves bilaterally. The reduced inspiratory force during TEST and direct phrenic stimulation is probably due to relaxation of the accessory muscles of respiration, particularly the intercostal muscles. Relaxation of these muscles makes the thoracic cavity more flexible, which offsets some of the inspiratory effort produced by the contracture of the diaphragm. Although the inspiratory force produced during TEST was not equal to that for a maximal spontaneous effort, it was consistently greater than that produced during quiet, normal breathing by the animal. This would suggest that there is a diminished ventilatory reserve during TEST, but the technique's capacity for ventilation should be adequate to provide life-sustaining levels of ventilation.